REMARKS/ARGUMENTS

Status of the Claims

Claims 61-69 were rejected. Claims 1-60 were previously canceled without prejudice or disclaimer. Claims 62, 63, and 65 have also been canceled to expedite prosecution. Applicants expressly reserve the right to file a continuation or divisional application or to take other such appropriate action to seek protection of the canceled subject matter.

Claims 61 and 64 have been amended to further prosecution and to more clearly define the invention. Support for these claim amendments can be found in the specification and claims as originally filed. See, for example, paragraphs [0073] and [0074]. Claim 69 has been amended to change claim dependency. No new matter has been added by way of the claim amendments. Claims 61, 64, and 66-69 are now pending in the present application. Reexamination and reconsideration of these claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 61-63 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,623,457 (hereinafter "the '457 patent"), U.S. Patent No. 6,309,650 (hereinafter "the '650 patent") in further view of U.S. Patent No. 5,830,463 (hereinafter "the '463 patent"). Claim 61 has been amended. Claims 62 and 63 have been canceled. This rejection is respectfully traversed with respect to amended claim 61.

Original claim 61 was drawn to a method for inducing an immune response to a flaviviral antigen in a subject comprising delivering a vaccine expressing the flaviviral antigen to a subject's skin using a device that targets the intradermal compartment of the subject's skin. To expedite prosecution, claim 61 has been amended to recite that the subject is a *human* subject and that *the device comprises at least one hollow microneedle that delivers the vaccine to the subject's skin to a depth of between 0.025 mm and 2.0 mm*. The rejection of claims 62 and 63 has been rendered moot by the cancellation of these claims.

As noted above, the Examiner has cited a number of references to establish the obviousness of claim 61. The '457 patent describes a transdermal delivery device including a plurality of microneedles for injecting a substance (e.g., a pharmaceutical agent) into or below the stratum corneum of the skin. The Examiner has acknowledged that the cited reference does not teach or suggest the use of the disclosed device for delivery of a flaviviral vaccine, as expressly recited in claim 61. See pages 2-3 of the Office Action mailed November 27, 2007. Moreover, in contrast to present claim 61 which expressly recites "using a device that targets the intradermal compartment of a subject's skin," the '457 patent actually *teaches away* from penetrating the dermal layer with its disclosed delivery device. See, for example, column 5, lines 21-24 and lines 53-55 of the cited reference. Specifically, the patentees maintain that avoiding delivery of the vaccine to the intradermal compartment is advantageous because it minimizes absorption of the vaccine into the bloodstream. See column 5, lines 21-24.

The '650 patent discloses a Japanese encephalitis vaccine comprising the attenuated virus and methods for its use. The cited reference, however, indicates that the Japanese encephalitis vaccine was delivered to test subjects by *intraperitoneal* injection. The '650 patent does not make reference to any other potential modes of delivering the vaccine to a subject and, in particular, does not teach or suggest targeting the vaccine to the intradermal compartment of a subject's skin at a depth of between 0.025 mm and 2.0 mm, as expressly recited in amended claim 61.

The Examiner has further cited the '650 patent in support of the obviousness of claim 61 but fails to comment in the Office Action on its relevance to the instant rejection. The '650 patent describes a yeast vehicle and its use as a delivery vehicle for pharmaceutical agents such as vaccines. The cited reference only describes using the yeast vehicles in *intraperitoneal* injections of test subjects and does not teach or suggest using the yeast vehicles to target the intradermal compartment of the subject's skin. See, for example, column 25, lines 50-52. In spite of the deficiencies noted above for each reference, the Examiner maintains that the cited references can be combined to arrive at the claimed method. Applicants respectfully disagree with the Examiner's conclusions.

Establishing a *prima facie* case of obviousness requires assessment of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), which provides the framework for applying the statutory language of § 103. Under the "Graham Factors," the Examiner is required to:

1. Determine the scope and content of the prior art;
2. Ascertain the differences between the prior art and the claims at issue;
3. Resolve the level of ordinary skill in the pertinent art; and
4. Consider any relevant secondary considerations.

Furthermore, a *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that the combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obvious requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. In the instant case, none of the cited references discloses the recited claim element of "using a device that targets the intradermal compartment of the subject's skin," either explicitly or implicitly. Thus, the disclosures of the cited references simply cannot be combined to arrive at the claimed method. As such, claim 61 is not obvious in view of the cited references, and the rejection under 35 U.S.C. § 103(a) should be withdrawn.

Furthermore, although the U.S. Supreme Court declined to permit a "rigid" application of the teaching-suggestion-motivation to combine (TSM) test to obviousness determinations, the Court did hold that the presence or absence of a teaching, suggestion, or motivation to combine the cited references provides a "helpful insight" regarding the obviousness of an invention. *KSR Int'l Co. v. Teleflex, Inc.*, KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1389 (U.S. 2007). The Supreme Court went on to acknowledge the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in way the claimed invention does" in an obvious determination. *Takeda Chemical Industries, Ltd. V. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007; citing *KSR Int'l Co. v. Teleflex, Inc.*). Although in the instant case the references do not teach all of the elements of amended claim 61 and, therefore, simply cannot be combined to produce the claimed method for

inducing an immune response to a flaviviral antigen, the Examiner has also merely provided broad conclusory statements and has failed to identify a sufficient reason for one of skill in the art to combine the cited references and to conclude that the present claim would be obvious in view of such a combination.

In the instant case, the Examiner has merely pieced together the claimed invention by citing references that allegedly teach elements of the claims. Accordingly, the Examiner appears to have "arrived" at the claimed method by citing references that teach claim elements without providing a sufficient *reason* to combine these references. The "helpful insight" provided by the TSM test actually points away from a finding of obviousness in this case. Applicants respectfully submit that at the time of filing, there was no reason for the skilled artisan to combine the cited references to practice the claimed method and no reasonable expectation of success in such a combination. The cited references, alone or in combination, do not provide any reason for one of skill in the art to induce an immune response to a flaviviral antigen in a human subject comprising delivering a vaccine expressing the flaviviral antigen to the subject's skin using a device that targets the intradermal compartment and that comprises at least one hollow microneedle that delivers the vaccine to the subject's skin at a depth of between 0.025 mm and 2.0 mm, as recited in amended claim 61.

In fact, as discussed above, the cited '457 patent actually *teaches away* from targeting a vaccine to the intradermal compartment of a subject's skin. Therefore, prior to the present invention the skilled artisan would not have had a reason to combine the cited patents. Accordingly, the lack of a *reason* to combine the cited references to arrive at the claimed method with a reasonable expectation of success provides further evidence that the claims are not obvious.

Given the lack of evidence of a reason to combine the references, it appears that the Examiner has engaged in impermissible "hindsight reconstruction" in formulating the present rejection. See *In re Fine*, 5 USPQ2d 1071, 1075 (Fed. Cir. 1988) (holding that "[o]ne cannot use hindsight reconstruction to pick and choose among disclosures in the prior art to deprecate the claimed invention") and *Graham v. John Deere Co.*, *supra* (stating the importance of guarding

against "slipping into hindsight and…resisting [the] temptation to read into the prior art the teachings of the invention in issue"). Therefore, in establishing obviousness, it is improper "to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

Accordingly, in light of the above remarks, Applicants respectfully request that the obviousness rejection of claim 61 under 35 U.S.C. § 103(a) be withdrawn.

Claims 64-69 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '457 patent, the '650 patent, the '463 patent, and in further view of U.S. Patent No. 6,361,524 (hereinafter "the '524 patent"). Claim 64 has been amended to clarify the invention, and claim 69 has been amended to change claim dependency. Claim 65 has been canceled. This rejection is respectfully traversed with respect to amended claims 64 and 66-69.

Original claim 64 was drawn to a kit for use in inducing an immune response to a flaviviral antigen comprising a vaccine expressing the flaviviral antigen and a device that targets the intradermal compartment of the subject's skin. To expedite prosecution, claim 64 has been amended to more clearly describe the "device" recited in the claim. Specifically, claim 64 now recites that the device comprises: 1) at least one microneedle that is supported by a hub portion and has a forward tip that extends away from the hub portion, and 2) a limiter portion that surrounds the microneedle and extends away from the hub portion toward the forward tip of the microneedle. Claim 64 further recites that the limiter portion comprises a flat skin engaging surface that extends in a plane perpendicular to an axis of the microneedle, and the forward tip of the microneedle extends beyond the skin engaging surface at a distance of between 0.5 mm and 2.0 mm. Support for this claim amendment can be found in the originally filed specification at, for example, paragraph [0074]. Claim 65 has been canceled to further prosecution, and, therefore, claim 69 (which originally depended from claim 65) was amended to correct dependency.

The teachings of the'457 patent, the '650 patent, and '463 patent were discussed in detail above and will not be reiterated here for brevity. The '524 patent discloses syringe assemblies for use in flushing intravenous (I.V.) catheters with traditional agents such as saline and anticoagulants to maintain access to the vein and integrity of the catheter. The syringe assemblies of the cited reference minimize the problems frequently associated with the prior art devices, particularly substantial pressure variations and the potential for accidentally drawing blood into the catheter during the flush procedure. The '524 patent, however, does not teach or suggest using the disclosed I.V. flush syringe assemblies to deliver *any* vaccine to the intradermal compartment of a patient's skin. In fact, the syringe assemblies described in the cited reference are designed to flush an existing catheter in a vein and, as such, would be inappropriate for targeting a vaccine or any pharmaceutical agent to the intradermal compartment of a subject's skin. Despite the deficiencies noted above for each of the cited patents, the Examiner maintains that the '457, '650, '463, and '524 patents can be combined to arrive at the claimed kits. Applicants respectfully disagree with the Examiner's conclusions.

Establishing a *prima facie* case of obviousness requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. See *In re Zenitz, supra.* As noted above, the patents cited by the Examiner do not teach or suggest a vaccine delivery device that targets the intradermal compartment of a subject's skin, in particular a device with the specific features set forth in amended claim 64. Accordingly, the disclosures of the cited references simply cannot be combined to arrive at the claimed kits.

Although in the instant case the '457, '650, '463, and '524 patents simply cannot be combined to produce the claimed kits, the Examiner has also merely provided broad conclusory statements and has failed to identify a sufficient reason that would have prompted the skilled artisan to combine the cited references and to conclude that the instant claims would be obvious in view of such a combination. Therefore, in light of the above remarks, the rejection of claims 64 and 66-69 under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

The Examiner is respectfully requested to withdraw the rejection of the claims. In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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